# STUDIES ON THE SYNTHESIS, OPTOELECTRONIC AND PHARMACOLOGICAL PROPERTIES OF SOME NOVEL HETEROCYCLIC COMPOUNDS

## *Synopsis*

**OF THE PH.D. THESIS TO BE SUBMITTED TO THE**

**MANGALORE UNIVERSITY**

**FOR THE AWARD OF THE DEGREE OF**

***DOCTOR OF PHILOSOPHY***

**IN**

**CHEMISTRY**

**By**

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**KARNATAKA, INDIA.**

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**Title of the Thesis : STUDIES ON THE SYNTHESIS, OPTOELECTRONIC AND PHARMACOLOGICAL PROPERTIES OF SOME NOVEL HETEROCYCLIC COMPOUNDS**

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# SYNOPSIS

Heterocyclic compounds hold the largest position in organic chemistry with enormous biological and industrial importance. Their utilization in agrochemicals, pharmaceuticals, cosmetics, plastics, reprography and so on are widely documented[1]. The foremost among them is their biological applications. Since heterocycles are scattered broadly across life, nature has accepted heterocycles as the core of biological systems. DNA and RNA which are the most vital components of living cells are based on heterocyclic compounds. Also, naturally occurring compounds like vitamins, hemoglobin, nucleic acids, alkaloids, etc contain heterocyclic rings.

Beginning of the Medicinal chemistry arouse when pharmacist, physicians and chemists isolated and purified the pharmacophore of medicinal importance from plants and animals' tissues. Most of the drugs bear heterocyclic rings[2]. The extraction and purification of heterocyclic compounds from nature is quite expensive and leads to negligible yield. Therefore, one of the key routes to develop drugs is *via* organic synthesis. Some of the well-known drug candidates which are in regular clinical use include sulphadiazine as an antibacterial agent, celecoxib as an anti-inflammatory drug, sumatriptan as an antimigraine agent[3], albendazole as an anthelmintic agent[4] and glitazones as an antidiabetic drugs.

Triazoles are nitrogen-containing five membered heterocyclic compounds, which have two isomers that differ in the position of nitrogen atoms, namely 1,2,3-triazole and 1,2,4-triazole. Drugs containing the triazole moiety are a key pharmacophore for many biological applications. 1,2,3-triazole exists in three tautomeric forms: 1*H*-1,2,3-triazole, 2*H*-1,2,3-triazole, and 4*H*-1,2,3-triazole. It also can act as the isostere of amide, ester, carboxylic acid and other heterocycles. Also, 1,2,3-triazole possess varied pharmacological properties such as anti-tubercular[5], anti-fungal[6], anti-tumor[7]and anti-bacterial[8].

1,2,4-Triazole exists in two tautomeric forms: 1*H* and 4*H*. In the last few years, 1,2,4-triazole derivatives have attracted the attention of many scientists in agricultural and medicinal fields because of their interesting structural features and biological activities[9]. These derivatives have diverse biological properties, which include anticancer[10], antitumor[11], antimicrobial[12], anti-inflammatory[13], antibacterial[14], antimalarial[15], antifungal[16], antiviral[17], antiproliferative[18], neuroprotective[19], pesticidal, herbicidal[20], antioxidant[21], anti-HIV[22], analgesic[23], molluscicidal[24]

and anticonvulsant effects[25]. The well-known marketed drugs that contain the 1,2,4-triazole moiety are voriconazole , alprazolam, trapidil, bromuconazole etc.

Benzimidazole is a bicyclic compound which consists of fusion between benzene and imidazole moiety. The most prominent benzimidazole derivative in nature is *N*-ribosyl-dimethlbenzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$[26]. Benzimidazole and its derivatives associated with diversified biological activities such as antimicrobial[27], anti-inflammatory[28], antiallergic[29], antioxidant[30], antitubercular[31], antitumoral[32], anthelmintic[33], antiviral[34] and antimalarial[35]. In addition, benzimidazoles exhibit similar structural properties with purine, which hinders bacterial nucleic acids and proteins[36]. The synthesis of 1,2-disubstituted benzimidazoles by "one-pot" nitro reductive cyclization method[37] has gained much attention as the reaction is aided by one of the cheaply available reducing agent called sodium dithionite. Due to short reaction time, easy workup and products with high yield, this method was found to be more advantageous over the stepwise synthesis.

Apart from benzimidazole moiety being a bioactive molecule in the pharmaceutical field, this moiety was also found to display exciting fluorescent and photophysical properties[38-40]. One of the best methods to enhance fluorescence properties, device efficiency and operational lifetime is to incorporate donor/acceptor strategy. This in turn depends on the number of holes (HT) and electron transporting (ET) moieties[41,42]. The design and synthesis of small bipolar molecules combining both electron-donating and electron-withdrawing groups in the same molecule enhance the fluorescence efficiency. Electron-donating moiety such as substituted 2-hydroxyphenyl acts as a hole-transporting component whereas electron-withdrawing moiety benzimidazole, behave as an electron – transporting acceptors[43].

Fused heterocycles have gained attention of many researchers in the recent years owing to check for better pharmacological agents. Noticeably, triazolothiadiazines formed by the combination of 1,2,4-triazoles and 1,3,4-thiadiazines play a key role as antiproliferative[44], antitubercular[45], tubulin inhibitor[46], antimicrobial[47], acetyl- and butyryl-cholinesterases and alkaline phosphatase inhibitors[48], anti-inflammatory[49], antihelmintic[50], analgesic[51], molluscicidal agents[52] and PDE4 inhibitors[53].

Thiazolidinones are thiazolidine derivatives which have an atom of sulfur at position 1, an atom of nitrogen at position 3 and carbonyl group at position 2, 4 or 5. Its presence in pencillin was the first recognition of its occurrence in nature[54]. Thiazolidinones derivatives are reported to possess anti-inflammatory[55] antiproliferative[56,57], antiviral[58], anticonvulsant[59,60], antifungal[61], and antibacterial[62] activities.

Inspired by the above studies, we aimed to synthesize some derivatives of 1,2,4-triazole, triazolo-thiadiazine, benzimidazoles and thiazolidinone to investigate their biological as well as fluorescent applications.

**Chapter 1: A review on synthesis and biological evaluation of simple and fused five membered heterocycles**

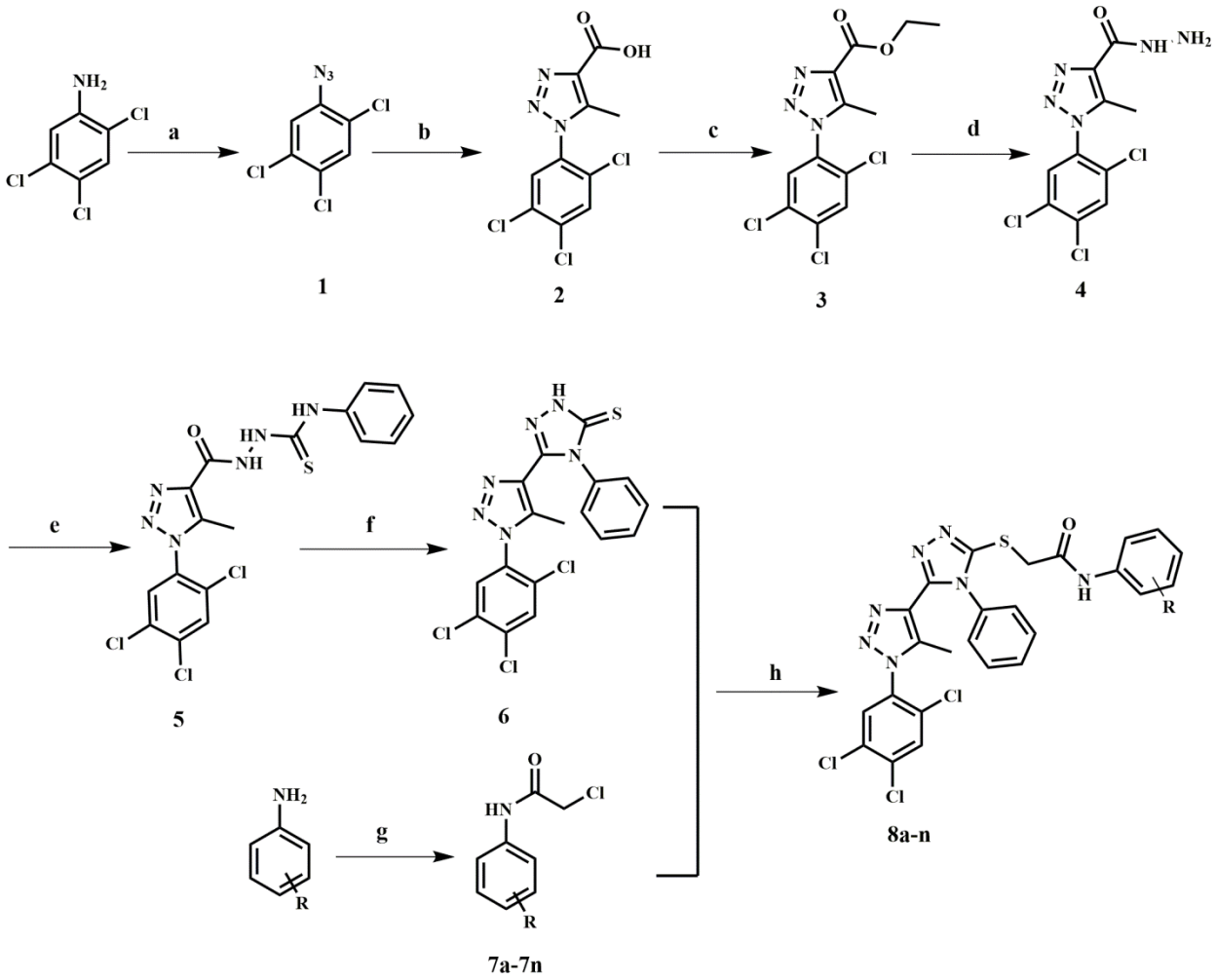
This is an introductory chapter, which deals with a brief account of synthesis and applications of some five membered simple and fused heterocyclic derivatives from the publications on chemical literature up to 2021.

**Chapter 2: Synthesis and biological evaluation of 1,2,5-trisubstituted 1,2,4-triazoles**

This chapter describes the synthesis and characterization of some novel 1,2,5-trisubstituted 1,2,4-triazoles as antimicrobial, anti-quorum and anti-inflammatory agents. The synthetic pathway followed to obtain target compounds (**8a-n**) is depicted in **Scheme 1**. At first, trisubstituted aniline was converted to corresponding azide (**1**) by treating with sodium nitrite and sodium azide in 1:1 mixture of Conc. HCl and water. The intermediate 5-methyl-1-(2,4,5-trichlorophenyl)-1*H*-1,2,3-triazole-4-carbohydrazide **(4)** was obtained by converting azides (**1**) to acid derivative of *N*-aryl-1,2,3-triazole (**2**), followed by esterification (**3**) and converting to corresponding carbohydrazide (**4**). Further intermediate **4** upon treating with phenyl isothiocyanate yielded carbothioamide (**5**), which underwent cyclization by refluxing with aqueous sodium hydroxide to furnish respective thione (**6**). This was treated with different *N*-(substituted phenyl)chloroacetamides (**7a-n**) to yield the target compounds (**8a-n)**.

All the compounds were characterized by elemental analyses, FTIR, $^{1}$H NMR, $^{13}$C NMR and mass spectroscopic techniques. These derivatives were screened for *in vitro* antimicrobial by disc diffusion method, *in vitro* antiquorum sensing activity against *C. violaceum*, *in vitro* anti-

inflammatory activity by bovine serum albumin method and *in vivo* anti-inflammatory activity by carrageenan induced rat paw edema model. Furthermore, docking studies of the active compounds were performed in order to explore the possible binding mode with CviR protein (PDB ID: 3QP5) of *C. violaceum*.




Where, R = 4-Cl-3-$NO_2$, 4-F, 3-$NO_2$, 3-F-2-$CH_3$, 3-Cl-4-F, 4-$CH_3$, 4-$OCH_3$, 4-Br-3-$CH_3$, 2-F, 3-Cl-2-$CH_3$, 3,4-$(CH_3)_2$, 2-$C_2H_5$-6-$CH_3$, 2-Br, 4-Br

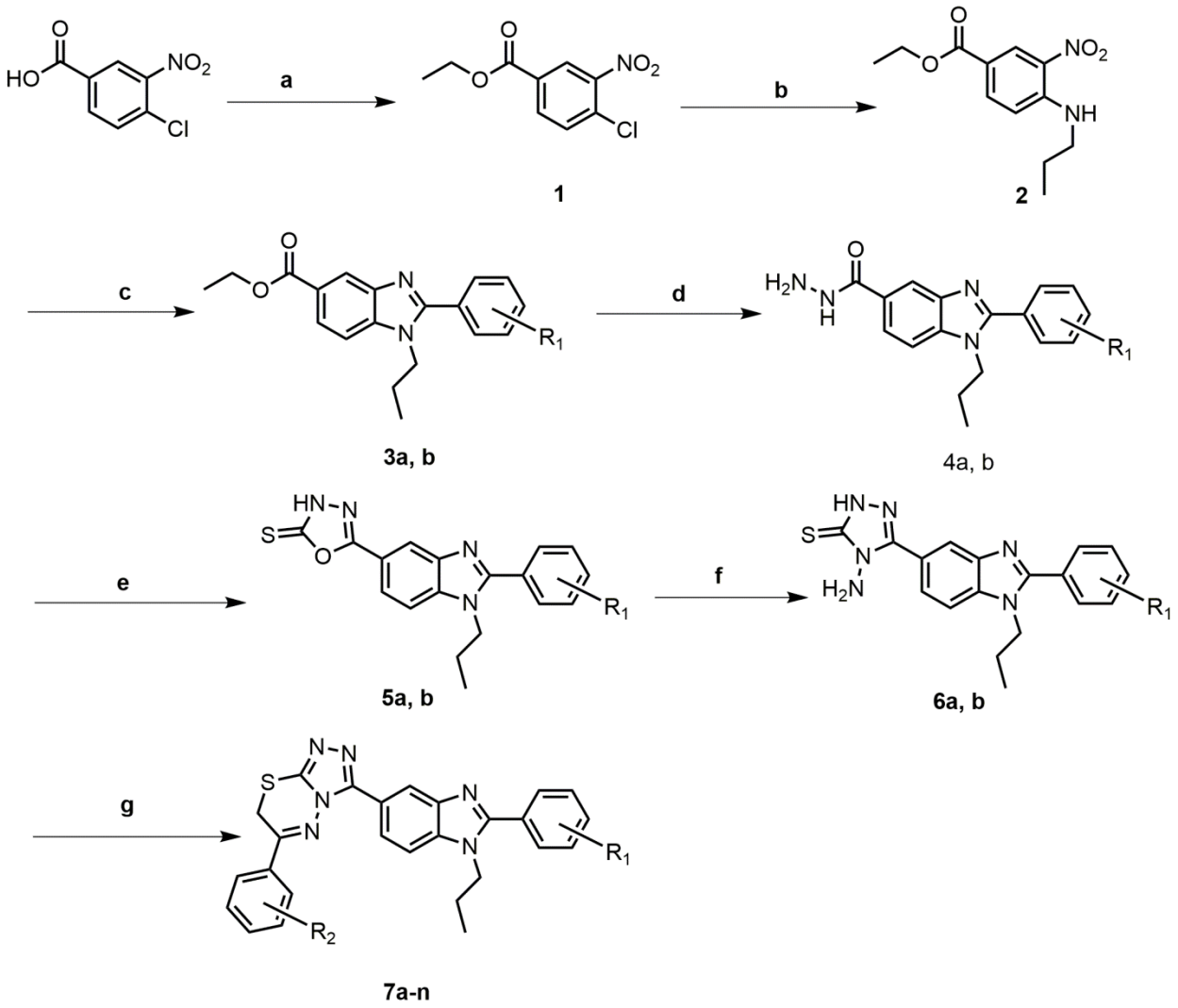
**Scheme 1:** The strategy for the preparation of 1,2,5-trisubstituted 1,2,4-triazoles, **8a-n**.

**Reagents and conditions:** (a) $NaNO_2/H_2O/HCl$, $NaN_3$, 0 °C to R.T. 16 h; (b) Ethylacetoacetate/EtOH, refluxed, 4 h; (c) EtOH/HCl, 90 °C, 16 h; (d) $NH_2NH_2.H_2O$/EtOH, 90 °C, 16 h; (e) PhNCS/EtOH, 90 °C, 8 h; (f) 5% NaOH, 100 °C, 3 h; (g) $ClCH_2COCl/Et_3N$/EtOH, 90 °C, 3 h; (h) $K_2CO_3/CH_3COCH_3$, R.T. 10 h.

## Chapter 3: Synthesis and biological evaluation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives embedded with benzimidazole moiety

This chapter deals with the synthesis and characterization of some [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives embedded with benzimidazole, followed by their biological evaluation as antioxidant agents. The strategy to obtain target compounds (**7a-n**) is depicted in **Scheme 2**. Initially, 4-chloro-3-nitrobenzoic acid was treated with a catalytic amount of conc. $H_2SO_4$ in ethanol to yield ethyl-4-chloro-3-nitrobenzoate (**1)**. Intermediate **1**, upon treating with n-propylamine as a nucleophile and triethylamine as a base in dry THF at room temperature, underwent nucleophilic substitution reaction to afford ethyl-3-nitro-4-(propylamino)benzoate (**2).** Intermediate **2** under treatment with sodium dithionite and substituted aldehydes allowed to undergo one-pot nitro reductive cyclisation reaction to yield ethyl-2-phenyl-1-propyl-1*H*-benzo[*d*]imidazole-5-carboxylate (**3a, b)**. Esters **3a**, **b** upon treating with hydrazine hydrate, afforded 2-phenyl-1-propyl-1*H*-benzo[*d*]imidazole-5-carbohydrazide (**4a, b)**. To the hydrazides in ethanol, KOH and $CS_2$ were added and refluxed for 8 h to produce intermediates **5a**, **b**, which were then treated with hydrazine hydrate in ethanol to yield 4-amino-5-(2-phenyl-1-propyl-1*H*-benzo[*d*]imidazol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**6a, b)**. With these thione intermediates in hand, it was treated with substituted phenacyl bromide under refluxing ethanol could achieve target compounds (**7a-n)**.

All the compounds were characterized by elemental analyses, FTIR, $^{1}$H NMR, $^{13}$C NMR and mass spectroscopic techniques. These derivatives were subjected to *in vitro* antioxidant activity. To determine the toxicity of active compounds, survival assay in *Drosophila melanogaster* was carried out. Also, physicochemical properties of the target compounds were studied.




Where, $R_1$ = 2,3-$Cl_2$, 3,4-$(OCH_3)_2$; $R_2$ = H, F, Cl, Br, Me, $OCH_3$, $NO_2$

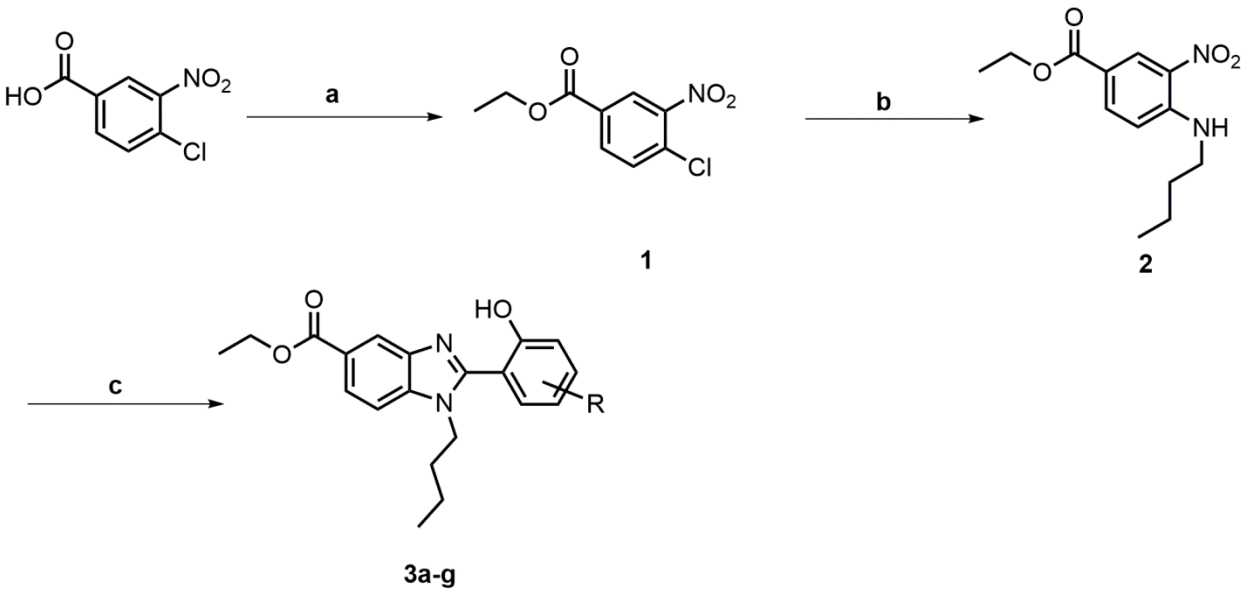
**Scheme 2:** The strategy for the preparation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives, **7a-n**.

**Reagents and conditions:** (a) $H_2SO_4$, ethanol, reflux, 16 h; (b) n-propylamine, triethylamine, R.T.; (c) $R^1$-Ph-CHO, sodium dithionite 90 °C, 3 h; (d) $NH_2NH_2.H_2O$/EtOH, 90 °C, reflux, 16 h; (e) $CS_2$/EtOH, KOH, 90 °C, 8 h; (f) $NH_2NH_2.H_2O$/EtOH, 100 °C, 8 h; (g) $R^2$-Ph-$CH_2$COBr/EtOH, 90 °C, 4 h.

## Chapter 4: Synthesis of benzimidazoles bearing hydroxyphenyl moiety and the study of their optoelectronic properties

This chapter describes the synthesis, characterization and optoelectronic properties of hydroxyphenyl-benzimidazoles. The synthetic route for target compounds **3a-g** is depicted in the **Scheme 3** which was obtained in three simple steps. The target compounds (**3a-g**) was obtained by converting 4-chloro-3-nitrobenzoic acid to ethyl 4-chloro-3-nitrobenzoate (**1**), followed by nucleophilic substitution reaction upon treatment with n-butylamine in the presence of triethylamine as a base in dry THF at room temperature to give ethyl 4-(butylamino)-3-nitrobenzoate (**2**). Consecutively, the target compounds was accomplished by sodium dithionite aided one-pot nitro reductive cyclisation of ethyl 4-(butylamino)-3-nitrobenzoate (**2**) with substituted salicylaldehyde in DMSO at 90 °C for 3 h. The obtained products were purified by recrystallisation in DMF. All these compounds can be stored for a longer time under the ambient conditions without any detectable degradation.

The formation of the products was confirmed by $^{1}$H NMR, $^{13}$C NMR, MS, FTIR, single crystal XRD and elemental analyses. Optoelectronic properties were determined by UV-Vis, solution and solid photoluminescence, quantum yield and fluorescence lifetime. The solvent-dependent absorption and emission were studied using both polar protic and polar aprotic solvents. The compound stability and electrochemical property were determined by thermal gravimetric analysis (TGA) and cyclic voltammetry (CV) respectively. The computational studies like Density-Functional Theory (DFT) and Molecular Electrostatic Potential (MEP) were conducted to provide important insights into the structure-property relationships.




Where, R = H, 5-F, 5-Cl, 5-Br, 4-OMe, 3,5-$Cl_2$, 3-OMe-5-Cl

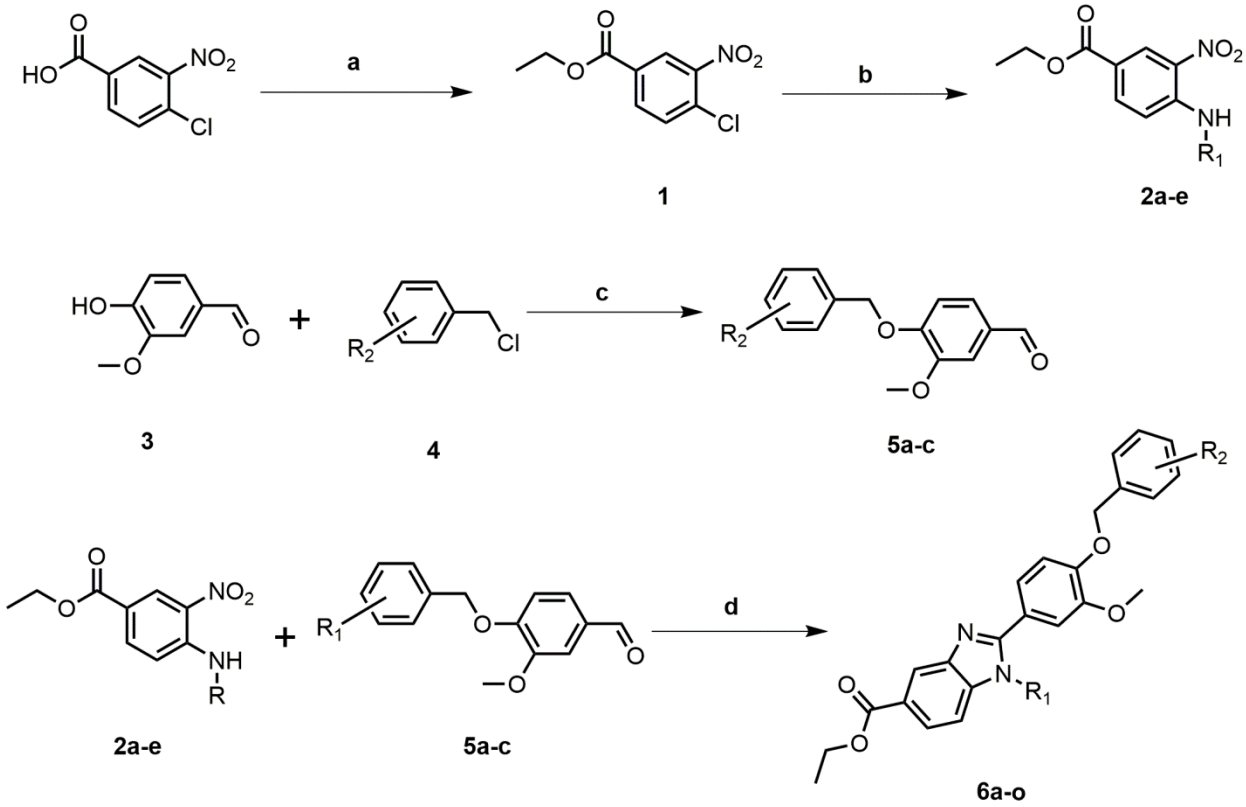
**Scheme 3:** The strategy for the preparation of hydroxybenzimidazoles, **3a-g**.

**Reagents and conditions**: (a) $H_2SO_4$, dry ethanol, reflux, 16 h; (b) n-Butylamine, triethylamine, R.T.; (c) substituted salicaldehydes, sodium dithionite, 90 °C, 3 h.

## Chapter 5: Synthesis and biological activities of novel 1,2-disubstituted-benzimidazole carboxylates

This chapter deals with the synthesis and characterization of 1,2-disubstituted benzimidazole carboxylate derivatives, followed by their biological evaluation as anti-inflammatory and anticancer agents. The synthetic strategy for the preparation of title compounds (**6a-o**) is depicted in **Scheme 4**. Initially, the two key scaffolds (i) ethyl 4-(alkylamino)-3-nitrobenzoate (**2a-e**) and (ii) substituted 4-(benzyloxy)-3-methoxybenzaldehyde (**5a-c**) required for the synthesis of target compounds were prepared separately. For the preparation of ethyl 4-(alkylamino)-3-nitrobenzoate (**2a-e**), ethyl 4-chloro-3-nitrobenzoate (**1**) was treated with primary amines of different alkyl chain lengths in THF. For the preparation of substituted 4-(benzyloxy)-3-methoxybenzaldehyde (**5a-c**), vanillin was allowed to react with potassium carbonate in DMF at room temperature. Later, substituted benzyl chlorides were added and refluxed the reaction mixture for 3 h. Finally, the two key scaffolds were clubbed together using previously optimized conditions (i.e. $Na_2S_2O_4$ (3eq) and DMSO solvent) to accomplish the target compounds (**6a-o**).

All the compounds were characterized by elemental analyses, FTIR, $^{1}H$ NMR, $^{13}C$ NMR and mass spectroscopic techniques. These compounds were screened for *in vitro* anticancer activity against three cell lines (HeLa, A559, HeK), *in vitro* anti-inflammatory activity by bovine serum albumin method and *in vivo* anti-inflammatory activity by carrageenan induced rat paw edema model.



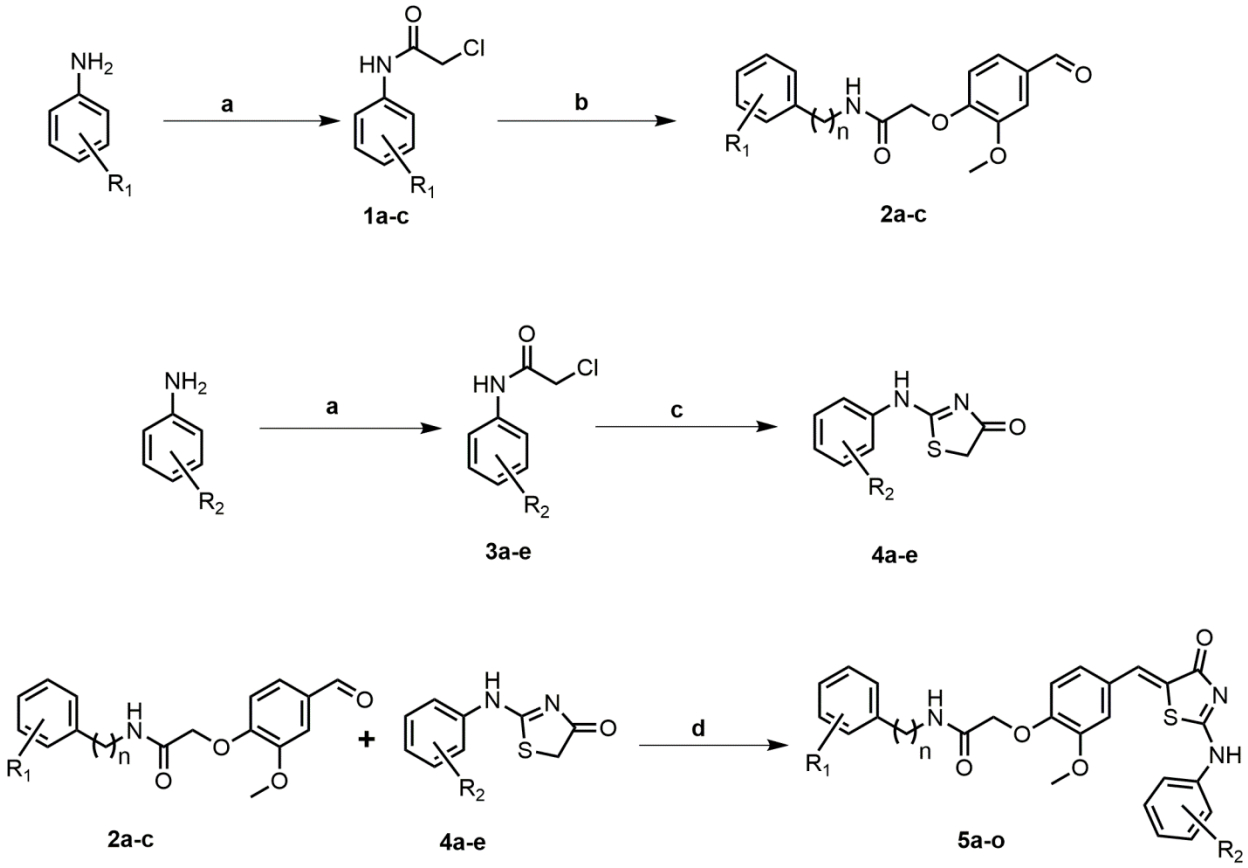

Where, $R_1$ = $CH_3$, $C_3H_7$, $C_4H_9$, $C_5H_{11}$, $C_6H_{13}$; $R_2$ = 4-Cl, 2,4-$Cl_2$, 3-F

**Scheme 4:** The strategy for the preparation of 1,2-disubstituted-benzimidazole carboxylate, **6a-o**. **Reagents and conditions**: (a) $H_2SO_4$, dry ethanol, reflux, 16 h; (b) n-Butylamine, triethylamine, R.T.; (c) $K_2CO_3$, DMF, reflux, 3 h; (d) substituted 4-(benzyloxy)-3-methoxybenzaldehyde, sodium dithionite, 90 °C, 3 h.

**Chapter 6: Synthesis and biological activities of novel thiazolidinone derivatives**

This chapter describes the synthesis of some novel thiazolidinone derivatives to explore their antibacterial and antioxidant activities. The general synthetic pathway to achieve title compounds is depicted in **Scheme 5**. Initially, substituted amines in DMF were treated with chloroacetyl

chloride at room temperature for 4-6 h to yield respective chloroacetamides (**1a-c** and **3a-e**). Now, the first key intermediate thiazolidine-4-one (**4a-e**) was achieved by refluxing chloroacetamides (**3a-e**) with ammonium thiocyanate in ethanol for 10 h. The second key intermediate 2-(4-formyl-2-methoxyphenoxy)-*N*-substituted-phenylacetamides (**2a-c**) was formed by reacting vanillin with potassium carbonate in DMF, followed by addition of chloroacetamides (**1a-c**). The reaction mixture was then heated to reflux for 1 h. Now in the final step, target compounds (**5a-o**) were achieved by clubbing two key scaffolds by means of Knoevenagel condensation using piperidine as a catalyst.




Where, $R_1$ = $CF_3$, 2-$C_2H_5$-6-$CH_3$, 2-Cl; $R_2$ = 4-F, 4-Cl, 3-$NO_2$, 3,4-$(CH_3)_2$, 2-$CH_3$-5-$NO_2$; n = 0, 1

**Scheme 5:** The strategy for the preparation of thiazolidinone derivatives, **5a-o**.

**Reagents and conditions**: (a) chloroacetyl chloride, DMF, R.T.; (b) $K_2CO_3$, DMF, reflux, 3 h; (c) $NH_4SCN$, ethanol, reflux 10 h; (d) piperidine, ethanol, reflux, 12 h.

All the compounds were characterized by elemental analyses, FTIR, $^{1}$H NMR and mass spectroscopic techniques. These compounds were evaluated for their antibacterial and antioxidant activities. Survival assay in *Drosophila melanogaster* was carried out to determine the toxicity of active compounds.

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**List of publications**

**A. Journal Publications**

1. **Sathyanarayana**, **R**., Poojary, B., Exploring recent developments on 1,2,4-triazole: Synthesis and biological applications, *J. Chin. Chem. Soc*., **2020**, *67*(4), 459-477.

2. **Sathyanarayana**, **R**., Poojary, B., Chandrashekarappa, R.B., Kumar, H., Merugumolu, V.K., Novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives embedded with benzimidazole moiety as potent antioxidants, *J. Chin. Chem. Soc*., **2020**, *67*(8), 1501-1516.

3. **Sathyanarayana**, **R**., Kumar, V., Pujar, G.H., Poojary, B., Shankar, M.K., Yallappa, S., Hydroxy-benzimidazoles as blue-green emitters: Synthesis, structural and DFT studies, *J. Photochem. Photobiol. A.*, **2020**, *401*, 112751.

4. **Sathyanarayana**, **R**., Bajire, S.K., Poojary, B., Shastry, R.P., Kumar, V., Chandrashekarappa, R.B., Design, synthesis, antibacterial and quorum quenching studies of 1, 2, 5-trisubstituted 1, 2, 4-triazoles, *J. Iran. Chem. Soc.*, **2020**, 18(5), 1-16.

5. **Sathyanarayana**, **R**., Poojary, B., Ethyl 1-butyl-2-(2-hydroxy-4-methoxyphenyl)-1*H*-benzo [*d*] imidazole-5-carboxylate, *Molbank*, **2021**, *2021*(1), M1192.

6. **Sathyanarayana**, **R**., Poojary, B., Srinivasa, S.M., Merugumolu, V.K., Chandrashekarappa, R.B., Rangappa, S., *In vitro*, *in vivo* and *in silico*-driven identification of novel benzimidazole derivatives as anticancer and anti-inflammatory agents, *J. Iran. Chem. Soc.*, **2021**, 1-17.

7. **Sathyanarayana**, **R**., Poojary, B., Bajire, S.K., Kumar, V., Shastry, R.P., Raghu, S.V., Design, synthesis and biological evaluation of novel thiazolidinone derivatives, *Asian J. Chem.*, **2021**, 33(10), 2379-2385.

8. Ganavi, D.; Ramu, R.; Kumar, V.; Patil, S.M.; Martiz, R.M.; Shirahatti, P.S.; **Sathyanarayana**, **R**.; Poojary, B.; Holla, B.S.; Poojary, V.; Kumari, K.N.; *In vitro* and *in silico* studies of fluorinated 2,3-disubstituted thiazolidinone-pyrazoles as potential α-amylase inhibitors and antioxidant agents, *Arch. Pharm.*, **2021**, e2100342.

**B. Papers presented in National/International Conferences**

1. **Reshma S.** and Boja Poojary (2019), Synthesis and Characterisation of Novel 1,2,5-trisubstituted 1,2,4-triazoles, National Conference on Synthetic, Spectroscopic and Structural Chemistry, Govinda Dasa College, Surathkal, Dakshina Kannada, Karnataka, 15-16th March.
2. **Reshma S.** and Boja Poojary (2019), Synthesis of novel [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives containing benzimidazole moiety, International Conference on Advanced Functional Materials for Energy, Environment and Health Care, Vijnana Bhavan Manasagangothri, Mysuru, Karnataka, 18-20th March.
3. **Reshma S**, Boja Poojary, Vijay Kumar Merugumolu, Revanasiddappa Bistuvalli Chandrashekarappa, Hemanth Kumar (2019), Synthesis of 1,2,5-trisubstituted 1,2,4-triazoles as Promising Anti inflammatory agents, International Conference on Advances in Chemical and Material Sciences held at Mangalore University, 17th -19th October.

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